

REMARKS/ARGUMENTS

By this Amendment, claims 38, 53, 55, and 64 are amended. Claims 46-48, 50, 66-71 have been withdrawn from consideration pursuant to a restriction requirement. Claims 38-42, 44-50, 53-57, 59-60, 62-74 are pending. Claims 38, 42, 44-45, 49, 53-57, 59-60, 62-65, 73 are pending and under consideration.

Citations to the Specification are directed to U.S. Patent Application Publication No. 2004/0265350 (Sambrook et al.).

Support for the amendments to the claims can be found throughout the Specification as filed, and specifically: Support for the limitation in claims 38 and 64 "the pores comprising a network of coalesced spheres" can be found in ¶[0018], which states:

characterised in that small bubbles of gas are introduced in the dispersion with agitation to form the foam and are allowed to cause to coalesce before the polymerisation of the monomeric material.

As a person having ordinary skill in the art will understand, bubbles are spherical, as such a configuration minimizes their surface area. Accordingly, the person having ordinary skill in the art understands that the method of production of the porous ceramic so described produces a network of coalesced spherical pores.

Support for the limitation in claim 64 for the limitation wherein the second material is "MTX" can be found in ¶[0030], which states:

According to this invention in one aspect there is provided a preformed porous ceramic carrier comprising an interconnected skeleton having pores the majority of which are in the range of from about 20 to about 1000 micron, the carrier having a density of less than 40% theoretical, the pores containing a second material therein, the rate of release of the second material from the carrier being controlled.

and ¶[0053] which states:

Methotrexate (MTX), the 4-amino, 10-methyl analogue of folic acid, remains the most widely used antifolate in cancer chemotherapy, with documented activity against leukaemia, breast cancer, head and neck cancer, lymphoma, urothelial cancer, choriocarcinoma and osteosarcoma. This class of agents represents the best characterised and most versatile of all chemotherapeutic drugs in clinical use. MTX is a tight binding inhibitor of dihydrofolate reductase((DHFR), a critical enzyme in maintaining the intracellular folate pool in its fully reduced form as tetrahydrofolates.

In addition, originally filed claim 64 states:

A preformed porous ceramic carrier comprising an interconnected skeleton having pores the majority of which are in the range of from about 20 to about 1000 micron, the carrier having a density of less than about 40% theoretical, the pores containing MTX, the rate of release of the MTX from the pores being controlled.

No new matter has been added by these amendments.

Favorable reconsideration is respectfully requested in view of the foregoing amendments and the following remarks.

Withdrawn Rejections

Withdrawal of the rejections as set forth by the Examiner on pages 2-5 of the Office Action is gratefully acknowledged.

Rejection under 35 USC 112 second paragraph

Claims 64 and 65 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is respectfully traversed.

The Examiner argues that claim 64 recites the limitation "the second material" in line 5 of

the claim, and that there is insufficient antecedent basis for this limitation in the claim. With acquiescing to the propriety of the Examiner's rejection, claim 64 has been amended herein to remove the recitation of "the second material" and replace it with "MTX".

Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Rejection under 35 USC 102(b)

Claims 38 - 42, 44, 45, 53, 54, 59, 60, 62, 63, 72 and 73 stand rejected under 35 U.S.C. 102(b) as being anticipated by Ishii (JP 04327525). This rejection is respectfully traversed.

The Examiner argues that Ishii discloses sustained release medicine-containing ceramic porous substances, and that the sustained release medicine-containing ceramic porous substances are capable of sustaining a medicine for a long period and preventing side effects due to concentrated elution of the medicine by applying a biodegradable substrate containing the medicine, dispersed and held therein to the inner wall surfaces in pores and on the outside surface of a ceramic porous substance. The Examiner further argues that Ishii teaches that the biodegradable substrate containing the medicine is chitin and its derivative or collagen, and that calcium phosphate-based ceramics, particularly tricalcium phosphate and hydroxyapatite are especially preferred. The Examiner argues that Ishii teaches that the porosity of the ceramic porous substance is preferably 30 - 95 % (i.e. a theoretical density of 5 - 70 %) and the average pore density is preferably within the range of 10 - 300 i.m. The Examiner further argues that the Ishii reference teaches that the base materials which may be used for holding drugs include chitin, chitosan, collagen, etc", and that the type of drug which is held includes antibiotics, anticancer drugs, protein drugs, an osteoplasty factor, etc (Office Action at pages 5-7) .

In *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051,

1053 (Fed. Cir. 1987) (MPEP 2131), the CAFC set forth that "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference". In the instant case, not every element of the claims is present in the Ishii reference.

Applicant has amended claim 38 in order to further distinguish the invention of the present application from the disclosure of Ishii. instant claim 38 is drawn to preformed porous ceramic carrier comprising an interconnected skeleton having pores the majority of which are in the range of from about 20 to about 800 micron, the carrier comprising block hydroxyapatite and having a density less than about 40% theoretical, the pores comprising a network of coalesced spheres the pores containing a second material deposited therein, the rate of release of the second material from the carrier being controlled by having the second material located within the pores in a degradable support.

Applicant submits that Ishii does not disclose a porous article having pores comprising network of coalesced spheres and having the claimed density. Ishii in fact provides a method for producing a porous ceramic article having a porosity of up to 95%. The method as disclosed in Ishii includes the steps of saturating a polyurethane sponge with a ceramic slurry and firing to burn out the polyurethane, and sinter the ceramic material (see Example 1). As a person having ordinary skill in the art would understand, such a method produces a ceramic body having a reticulated structure, i.e. the pore network is made up of a range of tubular cavities. Although Ishii describes another method of preparing a porous ceramic body having a density of less than 50%, namely that of firing a shape formed by mixing organic and ceramic powders (see paragraph [0015] and Example 2), a person skilled in the art would understand that this does not

create pores made up of a network of coalesced spheres. In fact, the pores correspond only to the cavities left behind by the organic particles themselves when they have been burned out by the firing step.

Instant claim 38 requires a ceramic carrier having a porosity of at least 60% (described as 40% density). It is therefore submitted that claim 38 as amended is novel in view of Ishii. In addition, it is further submitted that claims 39 to 42, 44, 45, 53, 54, 59, 60, 62, 63, 72 and 73 are, by virtue of their dependency on claim 38, novel in view of Ishii.

Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Rejection under 35 USC 103(a)

Claims 38 - 42, 44, 45, 53, 54, 59, 60, 62 - 65, 72 and 73 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Ishii (JP 04327525) in view of Itokazu et al. This rejection is respectfully traversed.

The Examiner argues that Ishii discloses sustained release medicine-containing ceramic porous substances containing a biodegradable substance which contains the medicine dispersed and held to the inner wall surfaces in pores and the outside surface of a ceramic porous substance, which may be an anticancer drug. The Examiner admits that Ishii does not specifically teach that the anticancer drug is MTX, but argues that Itokazu teaches porous apatite ceramics for the local delivery of chemotherapeutic agents. The Examiner further argues that it would have been obvious to one of ordinary skill in the art at the time of the instant invention to utilize MTX as the drug which was contained within the biodegradable support material (chitin or collagen) in the porous hydroxyapatite ceramic material disclosed by Ishii, because Ishii teaches that the drug may be an anticancer drug which is used in artificial bone for the therapy of

malignant tumor, etc., and because Itokazu teaches that MTX can be successfully released from porous apatite ceramic for the treatment of tumor (Office Action at pages 8-9).

The claims are patentable over the combination of Ishii and Itokazu et al. for the following reasons. The framework for the objective analysis for determining obviousness under 35 U.S.C. 103 is stated in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966). Obviousness is a question of law based on underlying factual inquiries. The factual inquiries enunciated by the Court are as follows: (A) Determining the scope and content of the prior art; and (B) Ascertaining the differences between the claimed invention and the prior art; and (C) Resolving the level of ordinary skill in the pertinent art. To establish prima facie obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 424 F.2d 1382, 1385 (CCPA 1970). MPEP 2143.03. It is important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does. (*KSR v Teleflex*, 12 S.Ct. 1727, 1740 (US 2007)). Here, Applicant submits that the combination of Ishii and Itokazu does not teach or suggest all the limitations of the claims.

Claim 38 is drawn to a preformed porous ceramic carrier comprising an interconnected skeleton having pores the majority of which are in the range of from about 20 to about 800 micron, the carrier comprising block hydroxyapatite and having a density less than about 40% theoretical, the pores comprising a network of coalesced spheres the pores containing a second material deposited therein, the rate of release of the second material from the carrier being controlled by having the second material located within the pores in a degradable support. Claim

64 is drawn to a preformed porous ceramic carrier comprising an interconnected skeleton having pores the majority of which are in the range of from about 20 to about 1000 micron, the carrier having a density of less than about 40% theoretical, the pores comprising a network of coalesced spheres, the pores containing MTX, the rate of release of the MTX from the pores being controlled by having the MTX located within the pores in a degradable support.

Claim 38, as amended, requires a porous ceramic article having a density of 40% or less and pores comprising a network of coalesced spheres. Such an article, as discussed above, is not described in Ishii. In fact, Ishii actually teaches away from producing any article other than one having a tubular porosity, as it is stated in Ishii at ¶[0015] that articles produced by a method different to that of saturating a polyurethane sponge with a ceramic slurry and firing exhibit only up to 50% porosity.

Moreover, ¶[0014] of Ishii points out that pore sizes larger than 300 μm cause any drug held within the porous article to be released too quickly. Once again, this teaches away from the invention recited in claim 38, which, in contrast, may have pores of up to 800 μm in diameter, and claim 64 which recites pores the majority of which are in the range of from about 20 to about 1000 micron. These larger pore sizes allow a greater quantity of drug to be held in each pore, while the join where two spheres have coalesced acts as a kind of throttle or collar to keep a drug held within the pores from leaching away quickly.

Additionally, the particular porous structure of the instantly claimed porous ceramic article helps to ensure that the pore network is totally interconnected, allowing for a far deeper fill (see ¶[0039] of the Application) than does the reticulated carrier of Ishii. This deficiency in Ishii teaching a porous ceramic carrier having a particular reticulated carrier porous

configuration, as opposed to the totally interconnected pore network as claimed, is not remedied by Itokazu.

Itokazu does not provide any specific detail as to the configuration of the pores of the ceramic carriers noted. However, it is disclosed in the final paragraph of page 536 that the hydroxyapatite carrier used had pores between 50 μ m and 300 μ m in diameter, further reinforcing the teaching of Ishii. Itokazu does not, then, contain motivation for the skilled person to move away from the teaching of Ishii to the larger pore sizes provided by the network of coalesced spheres of the invention recited in Claim 38 and 64. Claims 38 and 64 are therefore patentable over Ishii in view of Itokazu.

Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Rejection under 35 USC 103(a)

Claims 38 - 42, 44, 45, 53 - 55, 59, 60, 62, 63, 72 and 73 stand rejected under 35 U.S.C. 102(b) as being anticipated by Ishii (JP 04327525), in view of Laurencin et al. (US S,356,630). This rejection is respectfully traversed.

The Examiner argues that Ishii discloses sustained release medicine-containing ceramic porous substances containing a biodegradable substance which contains the medicine dispersed and held to the inner wall surfaces in pores and the outside surface of a ceramic porous substance. The Examiner admits that Ishii teaches collagen or chitin as a biodegradable support for the medicament, rather than PCPP-SA, as claimed. However, the Examiner argues that Laurencin discloses a system for the controlled or sustained release of bioactive substances which interact with local cell populations at a physiological site, and that it would have been obvious to one of ordinary skill in the art at the time of the instant invention to substitute PCPP-

SA as a functional equivalent for collagen as the biodegradable support which holds the medicament in the pores of the ceramic substance disclosed by Ishii. (Office Action at pages 10-11).

The claims are patentable over the combination of Ishii and Laurencin for the following reasons. The claims are set forth above, and the deficiencies of the teachings of Ishii have been discussed above. The deficiencies of Ishii in teaching a porous ceramic carrier having a particular reticulated carrier porous configuration, as opposed to teaching or suggesting the totally interconnected pore network as claimed, and additionally in not teaching or suggesting the claimed pore sizes, is not remedied by the addition of Laurencin. Laurencin teaches a system for the controlled release of a substance which interacts with local cell populations at a physiological site. Such systems include the provision of bioerodable polymers such as PCPP-SA. Laurencin is not, however, concerned with the configuration of the pores of hydroxyapatite carriers and is therefore unable to provide teaching for taking a person having ordinary skill in the art from Ishii to the invention of claim 38. Since claims 39 - 42, 44, 45, 53 - 55, 59, 60, 62, 63, 72 and 73 are dependent on claim 38, these claim are also patentable over the combination of Ishii and Laurencin.

Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Rejection under 35 USC 103(a)

The Office Action on page 11 indicates that "Claims 38 - 42, 44, 45, 53, 54, 56, 57, 59, 60, 62, 63, 72 and 73 are rejected under 35 U.S.C. 102(b) as being anticipated by Ishii (JP 04327525) in view of Genin (US 6,767,550)." It appears that this is actually a rejection under 35 USC 103(a), based on the combination of the references, and has been addressed as such, herein.

Clarification is requested.

Claims 38 - 42, 44, 45, 53, 54, 56, 57, 59, 60, 62, 63, 72 and 73 stand rejected under 35 U.S.C. 103(a) as being anticipated by Ishii (JP 04327525) in view of Genin (US 6,767,550). This rejection is respectfully traversed.

The Examiner argues that Ishii discloses sustained release medicine-containing ceramic porous substances containing a biodegradable substance which contains the medicine, including anticancer agents, dispersed and held to the inner wall surfaces in pores and the outside surface of a ceramic porous substance. The Examiner admits that Ishii does not specifically teach that the pores contain layers of medicament and degradable support, each layer being different from its neighbors, or alternating medicament-free and medicament-containing layers, but argues that Genin discloses hydroxyapatite based bioresorbable materials incorporated with anti-cancer agents to form an implant used for treatment against cancer, and that it would have been obvious to one having ordinary skill in the art at the time of the instant invention to provide the biodegradable support material which holds a medicament in the pores of the ceramic substance disclosed by Ishii in the form of alternating layers (Office action at pages 11-12).

The claims are patentable over the combination of Ishii and Genin for the following reasons. The claims are set forth above, and the deficiencies of the teachings of Ishii have been further discussed above. The deficiencies of Ishii in teaching a porous ceramic carrier having a particular reticulated carrier porous configuration, as opposed to teaching or suggesting the totally interconnected pore network as claimed, and additionally in not teaching or suggesting the claimed pore sizes, is not remedied by the addition of Genin.

Genin teaches the use of granular or block hydroxyapatite implants, which may be porous

or dense (column 6, line 35), for the delivery of anti-cancer agents. For instance, Genin describes a multilayered structure of pure and drug-loaded biomaterials for use as an implant for which the resorption rate is designed (see lines 19 to 21 of column 6).

However, Genin is concerned with ceramic implants in their green state – lines 66 to 67 of column 2 provide that the pressure used to form the implants ranges from 0.1 to 40 MPa, yet there is no description of any firing step. Indeed, the pores of the ceramic granules or discs described in Genin do not appear to be intrinsic in the structures of the articles, rather they are dependent on the presence of the drugs to be delivered in the pressing step (see Example 2 of column 8 of Genin).

Moreover, there is no disclosure of the overall density of the articles described in Genin. The pores of the present invention, which take the form of a network of coalesced spheres, could not be provided in a ceramic in its green state. This is because in applying the pressure necessary to form a green ceramic of some structural integrity, the bubbles which form the spherical pores would collapse.

Accordingly, Genin is not able to direct the skilled artisan from the drug-filled ceramic implants having tubular pores as described in Ishii to the implants having pores made up of a network of coalesced spheres as required by the invention of Claim 38.

It is therefore submitted that Claim 38 is inventive over Ishii in view of Genin. The Applicant further submits that claims 39 to 42, 44, 45, 53, 54, 59, 60, 62, 63, 65, 72 and 73 are, by virtue of their dependency on claim 38, inventive over Ishii in view of Genin.

Applicant submits that Claims 38 to 42, 44, 45, 53, 54, 59, 60, 62 to 65, 72 and 73 are patentable. Accordingly, reconsideration and withdrawal of the rejection is respectfully

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requested.

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For at least the reasons set forth above, it is respectfully submitted that the above-identified application is in condition for allowance. Favorable reconsideration and prompt allowance of the claims are respectfully requested.

Should the Examiner believe that anything further is desirable in order to place the application in even better condition for allowance, the Examiner is invited to contact Applicants' undersigned attorney at the telephone number listed below.

Respectfully submitted,

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